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Synthetic Applications and Methodological Developments of Donor–Acceptor Cyclopropanes and Related Compounds

Nicholas R. O'Connor[a], **John L. Wood**[b], and **Brian M. Stoltz**[a]

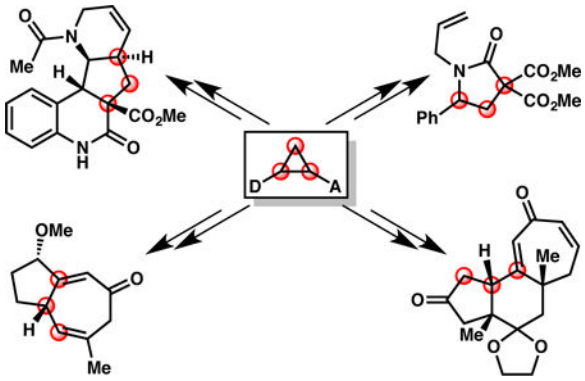
[a]The Warren and Katharine Schlinger Laboratory for Chemistry and Chemical Engineering, Division of Chemistry and Chemical Engineering, California Institute of Technology, 1200 E. California Blvd, MC 101-20, Pasadena, CA 91125 (USA), Fax: (626) 395-8436

[b]Department of Chemistry and Biochemistry, Baylor University, Waco, TX 76798 (USA)

Abstract

Donor–acceptor cyclopropanes are convenient precursors to reactive and versatile 1,3-dipoles, and have found application in the synthesis of a variety of carbo- and heterocyclic scaffolds. This perspective review details our laboratory's use of donor–acceptor cyclopropanes as intermediates toward the total synthesis of various natural products. We also discuss our work in the development of novel cycloadditions and rearrangements of donor–acceptor cyclopropanes and aziridines, as well as an example of an aryne insertion proceeding via fragmentation of a transient donor–acceptor cyclobutane.

Graphical Abstract



Keywords

cyclopropanes; rearrangements; fragmentations; cycloadditions; heterocycles

1. Introduction

Donor–acceptor cyclopropanes (**1**, Scheme 1), or those possessing one or more electron-donating groups and electron-withdrawing groups on adjacent carbons, are useful building blocks in organic synthesis.[1] Due to the presence of these vicinal charge-stabilizing groups and the strain inherent to the cyclopropane core, ring opening can occur under mild conditions. Typically, treatment with a Lewis acid at room temperature is sufficient to induce

carbon–carbon bond cleavage, leading to an all-carbon 1,3-dipole (**2**). These dipoles are generally quite versatile, having been shown to undergo nucleophilic trapping, electrophilic trapping, or dipolar cycloadditions to form a wide array of products (**3**–**6**, Scheme 1).

The acceptor groups are often carbonyl derivatives (with esters, ketones, and nitriles most common), although other electron-withdrawing groups, including sulfonyl, sufinyl, and phosphoryl, are occasionally used. Traditional donor groups are alkoxy, silyloxy, and amino substituents. Over the past decade, however, the use of aryl donor groups has become widespread, pioneered by the work of Kerr[2] and Johnson.[3] Aryl-substituted cyclopropanes are readily available in one or two steps from styrenes or benzaldehydes using straightforward methods.[1a] These compounds are typically more stable than cyclopropanes with heteroatom-based donors, and in some circumstances are capable of undergoing stereospecific reactions.[4]

Our laboratory's interest in donor–acceptor cyclopropanes was sparked during the PI's use of cyclopropane fragmentations (classified as electrophilic trapping in Scheme 1) as a method of ring expansion in the synthesis of K252a and the welwitindolinone C isothiocyanate core during his graduate studies in the Wood group. This perspective review describes this work in more detail below, and proceeds to examine our continued use of donor–acceptor cyclopropane fragmentations and cycloadditions toward the total synthesis of natural products. Our past and current efforts in this vein have also inspired the development of several new methods utilizing cyclopropane and aziridine rearrangements and cycloadditions, which are also discussed. Finally, we present a serendipitously discovered aryne C–C insertion reaction which is believed to proceed via fragmentation of a transient donor–acceptor cyclobutane intermediate.

2. Use of Donor–Acceptor Cyclopropanes as Intermediates in Natural Products Synthesis

2.1 Total Synthesis of K252a

Our interest in the use of donor–acceptor cyclopropanes as intermediates in natural products total synthesis began with the synthesis of K252a (**7**, Scheme 2) by one of us in the Wood laboratory at Yale University.[5] Isolated in 1985 by Sezaki and co-workers from a culture of the soil bacterium *Actinomadura* sp. SF-2370,[6] (+)-K252a was found to possess nanomolar inhibitory activity against protein kinase C.[7] Subsequent studies showed that structurally related compounds possess similar activity, and suggested these indolocarbazole alkaloids may have potential in the treatment of cancers[8] and neurodegenerative diseases.[9]

Stoltz, Wood, and co-workers envisioned accessing K252a (**7**) by late stage glycosylation of an indolocarbazole precursor **8**, itself constructed by coupling of diazolactam **11**[10] and 2,2'-biindole[11] (**10**, Scheme 2). Indoles had been functionalized at the C3-position by treatment with carbenes or metal carbenoids, with the reactions proceeding through cyclopropanation of the indole C2–C3 bond and subsequent by fragmentation.[12]

Extensive experimentation revealed that treatment of a mixture of **11** and **10** with 1 mol % rhodium(II) acetate in pinacolone at 120 °C furnished the desired indolocarbazole **8** in 62%

yield.[13] Although no intermediates could be observed by TLC or NMR, the reaction is presumed to proceed via the transient donor–acceptor cyclopropane **12** produced by cyclopropanation of the rhodium carbenoid onto an indole C2–C3 bond (Scheme 3). This cyclopropane is expected to rapidly fragment to form the more stable enol biindole **13**, which can undergo a 6π electrocyclic ring closure, followed by dehydrative aromatization to form **8**. Small amounts of hemiaminal **15** were also obtained in the reaction, and subjection of this material to xylenes at reflux or CSA resulted in quantitative conversion to **8**. It was postulated that this byproduct was formed from adduct **13**, supporting the proposed mechanism outlined in Scheme 3.

Indolocarbazole **8** was advanced to K252a by coupling with furanose **9** (synthesized in four steps from methyl diazoacetoacetate) using conditions inspired by McCombie.[14] The desired isomer of the two glycosylated indolocarbazoles was then deprotected using TFA and thioanisole to provide the target with a longest linear sequence of seven steps.

2.2. Synthesis of the Welwitindolinone Carbon Skeleton

Stoltz, Wood, and co-workers continued to pursue their interest in donor–acceptor cyclopropane intermediates in their efforts toward the carbon skeleton of the welwitindolinone alkaloids.[15] Isolated in the 1990s from various cyanobacteria, some welwitindolinone alkaloids act as P-glycoprotein P-170 inhibitors with multidrug-resistance reversing activity.[16] Stoltz and Wood planned to form the carbon skeleton of the most potent member of the family, *N*-methylwelwitindolinone C isothiocyanate (**16**, Scheme 4) by elaboration of oxindole **17**, itself formed by ring opening and further functionalization of a donor–acceptor cyclopropane derived from diazo compound **18**. This cyclopropane was to be synthesized from isatin (**20**) via intermediate **19**

In the forward direction, Wittig homologation of isatin (**20**) and cyclopropanation of the resulting olefin using a phosphorus ylide, followed by *N*-methylation produced stable cyclopropane **21**, containing one aryl donor group and two vicinal carbonyl-type acceptor groups (Scheme 5). The ethyl ester was converted to α-diazo ketone **19**, which upon treatment with rhodium(II) trifluoroacetate and Montmorillonite K-10 clay underwent an aryl C–H insertion step to afford tetracycle **22** in good yield.

Benzylic oxidation, tosylhydrazone formation, and elimination selectively formed the desired α-diazo ketone (**18**). Exposure of the corresponding rhodium carbenoid to allyl alcohol furnished cycloheptenone **24** in nearly quantitative yield. This reaction proceeds by initial insertion of the rhodium carbenoid into the O–H bond of allyl alcohol to form the transient cyclopropane **23**, which features a strong enol donor substituent at one position and a carbonyl acceptor group at a vicinal position.This unstable intermediate undergoes fragmentation to produce cycloheptenone **24**. Addition of ethynylmagnesium bromide and Claisen rearrangement gave enyne **25**, which was advanced to the welwitindolinone carbon skeleton (**17**) by Lindlar hydrogenation and ring closing metathesis.

2.3 Approach toward the Synthesis of Bielschowskysin

The Stoltz laboratory continued to investigate the strategy of cyclopropane fragmentation en route to larger carbocyclic rings in their approach toward the total synthesis of bielschowskysin (**26**, Scheme 6).[17] Isolated in 2004 from a Caribbean coral, **26** was found to possesses potent anticancer activity.[18] The simplified scaffold of **27** was chosen as a model system.

We planned to construct the highly functionalized core cyclobutane ring of **27** from donor–acceptor cyclopropane **29** by a ring opening-Michael addition cascade sequence proceeding through intermediate **28**. Cyclopropane **29** would be synthesized from diazoacetoacetate **30**, which in turn would be accessed from simple aryl bromide (**31**)[19] and enone (**32**)[20] building blocks.

In the forward direction, alcohol **33** was synthesized from **31** using a three-step sequence consisting of borylation,[21] Suzuki cross-coupling with vinyl iodide **32**,[22] and diastereoselective Luche reduction (Scheme 7). At this stage, optically pure material could be optained by the oxidative kinetic resolution protocol previously developed in our laboratory.[23] Advancement to diazoacetoacetate **30** was achieved through another three step sequence.[24] The key donor–acceptor cyclopropane **34** was obtained in moderate yield upon heating **30** with $Cu(TBS)_2$ in toluene or DCE.

At this point, we envisioned that acetate cleavage and oxidation of the resulting alcohol would form cyclopropane **29**, which would undergo the fragmentation-Michael addition cascade upon exposure to a Lewis acid. Unfortunately, acetate cleavage, oxidation, and treatment with lanthanum triflate in methanol produced cyclopentanol **38** (Scheme 8) rather than desired cyclobutane **27**. This occurs as the result of an undesired translactonization following acetate hydrolysis to give **35**. Oxidation and exposure to Lewis acid causes fragmentation of the cyclopropane to form a stabilized enolate and an extended oxocarbenium cation (**36**). Addition of one equivalent of methanol provides presumed intermediate **37**, which proceeds through hemiketal formation and transesterification to afford the observed cyclopentanol (**38**). Unfortunately, all attempts to avoid this undesired translactonization were unsuccessful, and our synthetic efforts concluded at this point. This effort highlights the tenuous nature of such reactive, strained, and sterically constrained donor–acceptor cyclopropane systems.

2.4. Synthesis of the Core of the Gagunin Diterpenoids

We again chose to investigate a donor–acceptor cyclopropane fragmentation strategy in our construction of the carbocyclic core structure of the gagunin diterpenoids.[25] The gagunin family of natural products, isolated in 2002 from the sea sponge *Phorbas* sp., are characterized by a highly oxygenated 5–6–7 tricyclic core containing two all-carbon quaternary stereocenters. Depending on the extent of core oxygenation, these diterpenoids exhibit varying levels of cytotoxicity.[26]

We planned to target these natural products (exemplified by gagunin E, **39**, Scheme 9) by late-stage cyclopentane formation and oxygenation of bicyclic diketone **40**. This compound

would be reached from triflate **41**, itself accessed from symmetrical precursor **42**, a key intermediate in our previously reported total synthesis of the related cyathane diterpenoids.[26]

In the forward direction, compound **42** was synthesized from diallyl succinate in two steps as a mixture of diastereomers.[27a] Subjection of this material to a double enantioselective decarboxylative allylic alkylation reaction[28] using conditions developed in our laboratory gave bis-allylated cyclohexane-1,4-dione **43** in good yield, good diastereoselectivity, and excellent enantioselectivity. Enol triflate formation afforded **41**, which was converted to tetraene **44** in four steps. Ring-closing metathesis produced **40**, containing the seven-membered ring of the gagunin core. A four-step sequence consisting of enone carbonate protection and allyl functional group interconversions delivered α-diazo ketone **45**.

Treatment of **45** with rhodium(II) acetate in dichloromethane gave cyclopropane **46** in good yield, and ring fragmentation with potassium carbonate in methanol furnished **47**, containing the 5–6–7 tricyclic core of the gagunin diterpenoids in 31% yield. This appears to be an uncommon example of the reactivity of a donor–acceptor cyclopropanes with a transiently formed enolate acting as the donor[29]. Interestingly, cyclopropane **50** was also isolated from the fragmentation step in 27% yield.This unexpected compound is presumed to arise from deprotonation of **47** and subsequent retro-norcaradiene rearrangement. Alternatively, **50** could be formed from **46** by carbonate cleavage, γ-deprotonation, and rearrangement.

2.5 Synthesis of the ABCD Ring System of Scandine

Having gained an appreciation for the utility of donor–acceptor cyclopropanes in synthesis, we planned to use a cyclopropane-olefin cycloaddition to construct the central C ring of scandine (**51**, Scheme 11), the parent compound of the *Melodinus* alkaloids.[30,31] Although they possess no known biological activity, these compounds attracted our interest due to their structural complexity, specifically the highly congested cyclopentane (C) ring.

Our original retrosynthesis is shown in Scheme 11. Late-stage E ring formation by carbenoid C–H insertion simplifies the target to tetracycle **52**, which could arise from cyclopentane **53** by nitro reduction, lactam ring closure, allylation, and selective ring-closing metathesis.[32] This cyclopentane could be formed by a palladium-catalyzed formal (3 + 2) cycloaddition between donor–acceptor cyclopropane **55** and nitroolefin **54**.[33]

Unfortunately, despite significant effort, the synthesis of divinyl cyclopropane **55** proved elusive.[34] A revised retrosynthesis was developed, beginning with a monovinyl cyclopropane in the (3 + 2) reaction, and relying on a late-stage C–H vinylation to install the second vinyl group. The use of stable vinylcyclopropane **56** (Scheme 12) relied upon the known reactivity of such compounds to unveil their donor–acceptor reactivity upon treatment with palladium(0) complexes.[33]

In the forward sense, exposure of known monovinyl cyclopropane **56**[35] and commercially available dinitrostyrene **54** to a palladium(0) phosphine complex afforded nitrocyclopentane **57** in good yield as a mixture of diastereomers (Scheme 12). Treatment of the mixture with zinc dust in acetic acid resulted in reduction of both nitro groups and subsequent

lactamization to afford quinolone **58** as a 2:1 mixture of diastereomers. The desired minor diastereomer (**58b**) was allylated under reductive amination conditions affording **59**. Amine protection and ring-closing metathesis furnished tetracycle **60** in good yield. Although **60** does not contain the vinyl group present in the natural product, we were able to build four out of the five rings in only six steps from commercial sources.

3. Development of Novel Reactions of Donor–Acceptor Cyclopropanes and Activated Aziridines

3.1. Synthesis of Fused Carbocycles by a Tandem Wolff–Cope Rearrangement

Natural products containing fused 5–7 and 6–7 ring systems are of considerable interest to the synthetic community due to their biological potential.[36] Inspired by complex seven-membered-ring-containing natural products like guanacastepene A (**61**, Scheme 13),[37] we devised a novel approach to the fused cycloheptadienone scaffold **62**, which could be viewed as a synthetic intermediate en route to these targets. This scaffold could conceivably arise through a ketene-Cope rearrangement of a divinyl cyclopropane such as **63**. While compounds like **63** do not fit the typical structural motif of a donor–acceptor cyclopropane, they are quite reactive. For any asynchronous reactions of these compounds, it is possible to envision the transition state featuring vicinal positive and negative charge stabilization, as is the case for most reactions of traditional donor–acceptor cyclopropanes. If the ketene moiety of **63** were to be accessed from an α-diazo ketone (**64**), it might be possible to form the desired cycloheptadienones in one pot through a tandem Wolff–Cope rearrangement.[38]

Donor–acceptor cyclopropane **64a** was synthesized from methyl acetoacetate and sorbyl alcohol, and was treated with a variety of conditions known to effect Wolff rearrangements. Extensive optimization revealed that the use of silver benzoate and triethylamine with sonication in THF at 45 °C resulted in nearly quantitative yield of the desired fused cycloheptadienone product **65a** as a single diastereomer (Scheme 14).

The substrate scope of the reaction is shown in Scheme 14. A range of hydroxyl protecting groups were tolerated (**64a–c**). Compounds containing a 1,1-disubstituted olefin (**64d**) or a monosubstituted olefin (**64e** and **64g**) were also competent substrates. Finally, a tricyclic product (**65f**) and a 6–7 ring system (**65g**) could be formed in excellent yields. Interestingly, photochemical conditions were necessary to achieve high yields with the substrates containing monosubstituted olefins (**64e** and **64g**).

Treatment of substrate **64a** with the photochemical conditions shown in Scheme 14 resulted in the isolation of the fused cyclopentenone product **65h** in good yield after a prolonged reaction time. This product is proposed to arise from a Norrish type I fragmentation of cycloheptadienone **65a**, followed by intramolecular radical recombination, resulting in a net 1,3-acyl migration process.[39]

The substrate scope of the tandem Wolff–Cope–1,3-acyl shift process is also shown in Scheme 14. As with the simpler Wolff–Cope rearrangement, this reaction is successful on substrates incorporating a variety of hydroxyl protecting groups (**64a–c**) and olefin substitutions (**64h**). This reaction is able to synthesize α-quaternary cyclopentenone **65k** in

excellent diastereoselectivity. Finally, access to both the 5–5 (**65h–j**, **65k**) and 5–6 (**65l**) fused ring systems is possible in good yields and diastereoselectivities.

3.2. Lewis Acid Mediated (3 + 2) Cycloadditions of Donor–Acceptor Cyclopropanes with Heterocumulenes

Inspired by our use of a donor–acceptor cyclopropane cycloaddition toward the construction of the scandine ABCD ring system, we have recently studied Lewis acid mediated cycloadditions of donor–acceptor cyclopropanes with heterocumulenes for the synthesis of five-membered heterocycles.[40,41] Similar cycloadditions of cyclopropanes with alkoxy donor groups were previously known, although the products were formed in low yield.[42] Furthermore, control of product stereochemistry was only possible through diastereoselective reactions making use of stereocenters remote from the site of reactivity. Inspired by the work of Johnson,[4a] Kerr,[4b] and others,[43,33b] we hoped that the use of aryl donor groups would allow for an enantiospecific reaction, occurring with transfer of stereochemical information at the benzylic position. This would enable rapid access to enantioenriched heterocyclic building blocks.

An investigation of Lewis acid, solvent, and temperature revealed that high yields of thioimidates (**67**, X=S) could be obtained in the reaction of allyl isothiocyanate with various donor–acceptor cyclopropanes (**66**) if stoichiometric tin(II) triflate in dichloromethane at 23 °C was used. The scope of the reaction is shown in Scheme 15. Cyclopropanes containing electron-rich donor groups were found to be the most reactive (furnishing products **67b**, **67e**, and **67g**). Cyclohexyl isothiocyanate was also found to be a competent dipolarophile (**67l**). Surprisingly, the isomeric thiolactams were never observed, providing complementarity to previously known reactions of alkoxy-substituted cyclopropanes with isothiocyanates.[42c,d].

Replacing the isothiocyanate with a carbodiimide allowed facile access to amidine products (**67m–s**). Examination of the scope of this reaction (Scheme 15) revealed that the carbodiimides were more reactive than the isothiocyanates, resulting in product formation even when combined with cyclopropanes unreactive with isothiocyanates (**67r**). Dialkyl- (**67m–p**), diaryl- (**67s**), and disilyl-carbodiimides[44] (**67q**, **67r**) were all well tolerated.

Isocyanates were relatively unreactive in the tin-mediated conditions, but a screen of alternative Lewis acids showed iron(III) chloride as capable of recovering reactivity. In contrast to the reactions with isothiocyanates, only lactam products (**68a–d**) and not imidates were formed. The scope of the reaction is shown in Scheme 15.

A study of the cycloadditions on an enantioenriched cyclopropane showed that while the iron-mediated conditions resulted in racemic product, the tin-mediated reactions produced the desired heterocycles in high ee, with those substrates reacting fastest giving the product with greatest enantiopurity (Scheme 16). X-ray crystallographic analysis revealed that the reaction of (*S*)-**66a** with diisopropylcarbodiimide proceeds with inversion of configuration at the benzylic position. These observations on the reaction stereochemistry, along with the noted increased reactivity of electron-rich dipolarophiles and cyclopropanes with more electron-rich donor groups, have led to a proposed mechanism for the reactions of donor–

acceptor cyclopropanes with isothiocyanates and carbodiimides (Scheme 16). Analogous to the mechanism proposed by Johnson and co-workers for the cycloadditions of donor–acceptor cyclopropanes with aldehydes,[45,46] we postulate activation of the substrate with the Lewis acid forms a highly reactive intermediate with a weakened C–C bond that retains the configurational information of the starting material (**69**). An S_N2-like attack of the dipolarophile at the benzylic stereocenter occurs with inversion of configuration, and the product of this step (**70**) undergoes ring closure to provide the observed heterocycles (**67**).

3.3. Stereoselective Lewis Acid Mediated (3 + 2) Cycloadditions of Activated Aziridines with Heterocumulenes

In addition to our work on cycloadditions of donor–acceptor cyclopropanes with heterocumulenes, we sought access to more highly nitrogenated heterocycles by replacing the cyclopropanes with related activated aziridines.[47] While these types of reactions were known at the outset of this work, there existed few examples using easily derivatizable *N*-sulfonylaziridines,[48] and only a single example of a stereoselective reaction.[49]

An initial examination of several Lewis acids showed that while tin(II) triflate was not able to promote the reaction between *N*-tosyl-2-phenylazridine (**71a**) and allyl isothiocyanate, the use of zinc(II) halides resulted in the clean formation of desired iminothiazolidine **72a** (Scheme 17). Zinc(II) bromide was chosen over the other zinc(II) halides due to its slightly superior yields and shorter reaction times.

The substrate scope of the reaction is shown in Scheme 17. A variety of aryl rings at the azridine 2-position (corresponding to the aryl donor group of the analogous donor–acceptor cyclopropanes) were tolerated, including those possessing electron-donating (**71b**, **71c**) and electron-withdrawing (**71d**, **71e**, **71g**, **71h**) groups. Primary and secondary alkyl isothiocyanates were successful dipolarophiles, producing iminothiazolidines **72k** and **72l** in excellent yields. Aryl isothiocyanates of varying electronics were also found to smoothly deliver the desired products (**72m–o**). The influence of the activating group on the aziridine nitrogen (corresponding to the acceptor group on the analogous donor–acceptor cyclopropane) was also explored, with a variety of sulfonyl substituents being well tolerated (affording **72p–r**). Interestingly, while the unprotected aziridine was converted to the product (**72s**) in good yield, *N*-alkyl-or *N*-acylaziridines were unreactive (**72t–v**). Carbodiimides also proved to be compatible with the reaction conditions, providing access to iminoimidazolidines. Disilylcarbodiimide[50] (**73a**), diphenylcarbodiimide (**73b–d**), and a dialkylcarbodiimide (not shown) all reacted to form the products in moderate to excellent yields.

During the examination of the scope of aziridine-isothiocyanate reactions, we observed that a *trans*-2,3-disubstituted aziridine reacted with allyl isothiocyanate to form the *cis*-4,5-disubstutited iminothiazolidine with exclusive diastereoselectivity (not shown). The apparently complete inversion of configuration at the benzylic position suggested the feasibility of a stereospecific variant of this reaction.

Exposure of enantioenriched *N*-tosyl-2-phenylazridine (*R*)-**71a** to allyl isothiocyanate and zinc(II) bromide resulted in isolation of the product iminothiazolidine (*S*)-**72a** in 42% ee.

Switching to zinc(II) chloride provided a small increase in product ee, and increasing the amount of isothiocyanate to 10.0 equivalents increased the ee of the product to 94% (Scheme 18, entry 1).

In addition to allyl isothiocyanate, the stereoselective reaction was tolerant of primary (entry 2) and secondary (entry 3) alkyl isothiocyanates, although use of a tertiary isothiocyanate formed the product (entry 4) in diminished yield and enantiopurity. Aryl isothiocyanates of varying electronics were also tolerated, providing products in excellent yields with moderate to good retention of enantiopurity (entries 5–7). Changing the sulfonyl group on the aziridine nitrogen had minimal effect on the product enantiopurity (entries 8–10), but the unprotected aziridine suffered from poor reactivity and gave the product in low ee (entry 11).

Our mechanistic proposal is analogous to that invoked in our previous work with donor–acceptor cyclopropanes. Coordination of the substrate with the Lewis acid forms a highly reactive intermediate with a weakened C–N bond that retains the configurational information of the starting material. The product is then formed by an S_N2-like attack of the dipolarophile at the benzylic *stereocenter* and subsequent ring closure. This proposal is supported by the greater reactivity of aziridines with electron-rich aryl groups and more strongly electron-withdrawing sulfonyl groups on the nitrogen. Inversion of configuration at the benzylic position is also consistent with this mechanism.

4. Development of a Benzyne Acyl-Alkylation Reaction Proceeding through Presumed Donor–Acceptor Cyclobutane Intermediates

During efforts directed toward the arylation of enolates with benzyne to form all-carbon quaternary stereocenters, we found that treatment of β-ketoester **75** with benzyne (**77**, generated in situ from **74** and fluoride) unexpectedly resulted in the formation of disubstituted arene **76** in moderate yield.[51] This represented the first mild and direct example of the insertion of benzyne into a β-ketoester carbon–carbon bond,[52] and is likely produced by fragmentation of transiently generated donor–acceptor cyclobutane **79** (Scheme 19).

This reactivity of benzyne with β-ketoesters proved to be quite general, and the scope of acyl-alkylation products produced is shown in Scheme 20. A variety of β-ketoesters were tolerated, including those containing branching or heteroatom-containing groups at the γ-position (providing products **82a–f**). β-Ketoesters derived from bulky and complex alcohols also afforded the acyl-alkylation products in good yield (**82g** and **82h**). Substituted arynes could also be used, furnishing **82i–k** in good to excellent yields. Finally, cyclic β-ketoesters were also capable substrates, reacting to give ring expansion products **82l–p**, in moderate yields, representing a novel route to medium-sized rings. We have demonstrated the utility of this aryne insertion reaction in several total syntheses.[53] Furthermore, our mechanistic hypothesis has been invoked by numerous groups in recent disclosures of aryne insertion reactions.[54]

5. Summary

Donor–acceptor cyclopropanes and related compounds like donor–acceptor cyclobutanes and activated aziridines have been used for decades to rapidly transform simple starting materials to complex products. Recent developments in the use of aryl donor groups have led to a resurgence of interest in these useful building blocks.

This perspective review has described our laboratory's use of donor–acceptor cyclopropanes and related compounds in both natural products synthesis and methodological developments over the past 15 years with inspiration dating into the early 1990s. Specifically, we have described the origin of our interest in the area with Stoltz and Wood's use of cyclopropane fragmentation strategies in the syntheses of K252a and the welwitindolinone C isothiocyanate core, as well as our continued use of these reactions in our efforts toward the synthesis of bielschowskysin and the gagunin terpenoids. We have also presented the application of a donor–acceptor cyclopropane-olefin cycloaddition reaction in the synthesis of the ABCD ring system of the *Melodinus* alkaloids. Additional efforts in the application of donor–acceptor cyclopropanes to natural products synthesis are currently underway in our laboratory.

As is the case in many laboratories, our endeavours in total synthesis often inspire the development of new methods.[55] In this case, our use of a donor–acceptor cyclopropane (3 + 2) cycloaddition toward scandine and other *Melodinus* alkaloids initiated further investigations into related reactivity, culminating in our reports of the cycloadditions of donor–acceptor cyclopropanes and activated aziridines with heterocumulenes. Additionally, in the course of unrelated synthetic studies, we discovered an aryne C–C insertion process presumably proceeding through a transient donor–acceptor cyclobutane intermediate. We look forward to the continued exploration of novel strained ring reactivity uncovered in our efforts in natural products synthesis.

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Biography

Nicholas R. O'Connor received a B.A. in chemistry from Macalester College in 2011, conducting research with Professor Rebecca C. Hoye. He then moved to the California Institute of Technology and began his doctoral studies under the direction of Professor Brian M. Stoltz. His graduate research focuses on the cycloadditions of strained rings and the application of these reactions to natural product synthesis.

John L. Wood was born on December 4, 1961 in Keokuk, IA. He received a B.A. degree from the University of Colorado in 1985 and a Ph.D. from the University of Pennsylvania in 1991 under the direction of Amos B. Smith, III. In 1991 he moved to Harvard University as an American Cancer Society postdoctoral fellow and continued studying natural products synthesis in the laboratories of Stuart Schreiber. He joined the faculty at Yale University in 1993 as an Assistant Professor and was promoted to Full Professor in 1998. In 2006, Professor Wood moved from Yale to join the faculty at Colorado State University as the Albert I. Meyers Professor of Chemistry. In 2013 Professor Wood moved to Baylor

University where he is currently the Robert A. Welch Distinguished Professor of Chemistry and a Cancer Prevention and Research Institute of Texas Scholar.

Brian M. Stoltz was born in Philadelphia, PA in 1970 and obtained his B.S. degree from the Indiana University of Pennsylvania in Indiana, PA. After graduate work at Yale University in the laboratories of John L. Wood, and an NIH postdoctoral fellowship at Harvard in the Corey laboratories, he took a position at the California Institute of Technology. A member of the Caltech faculty since 2000, he currently is a Professor of Chemistry. His research interests lie in the development of new synthetic methodology for general applications in synthetic chemistry.

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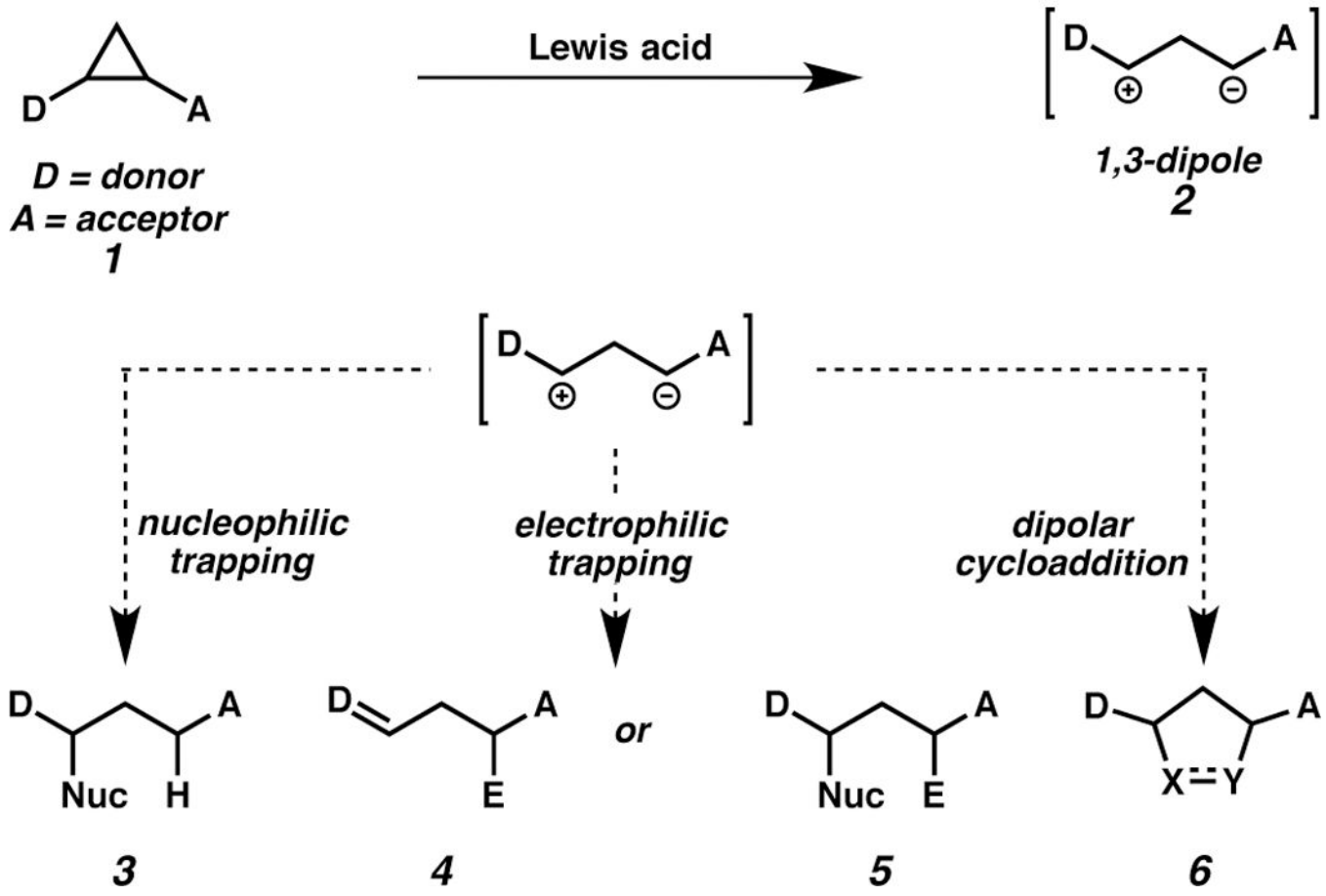
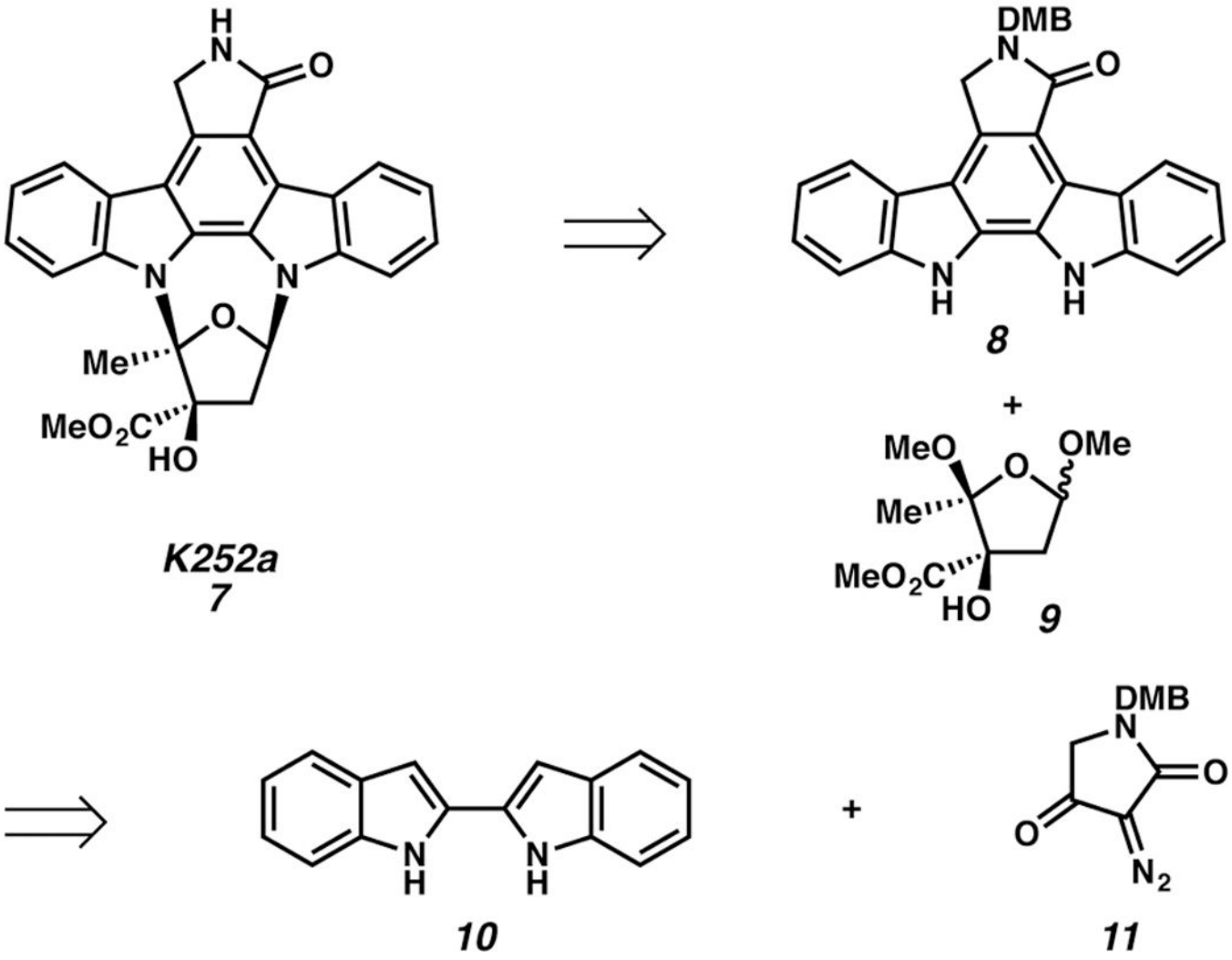
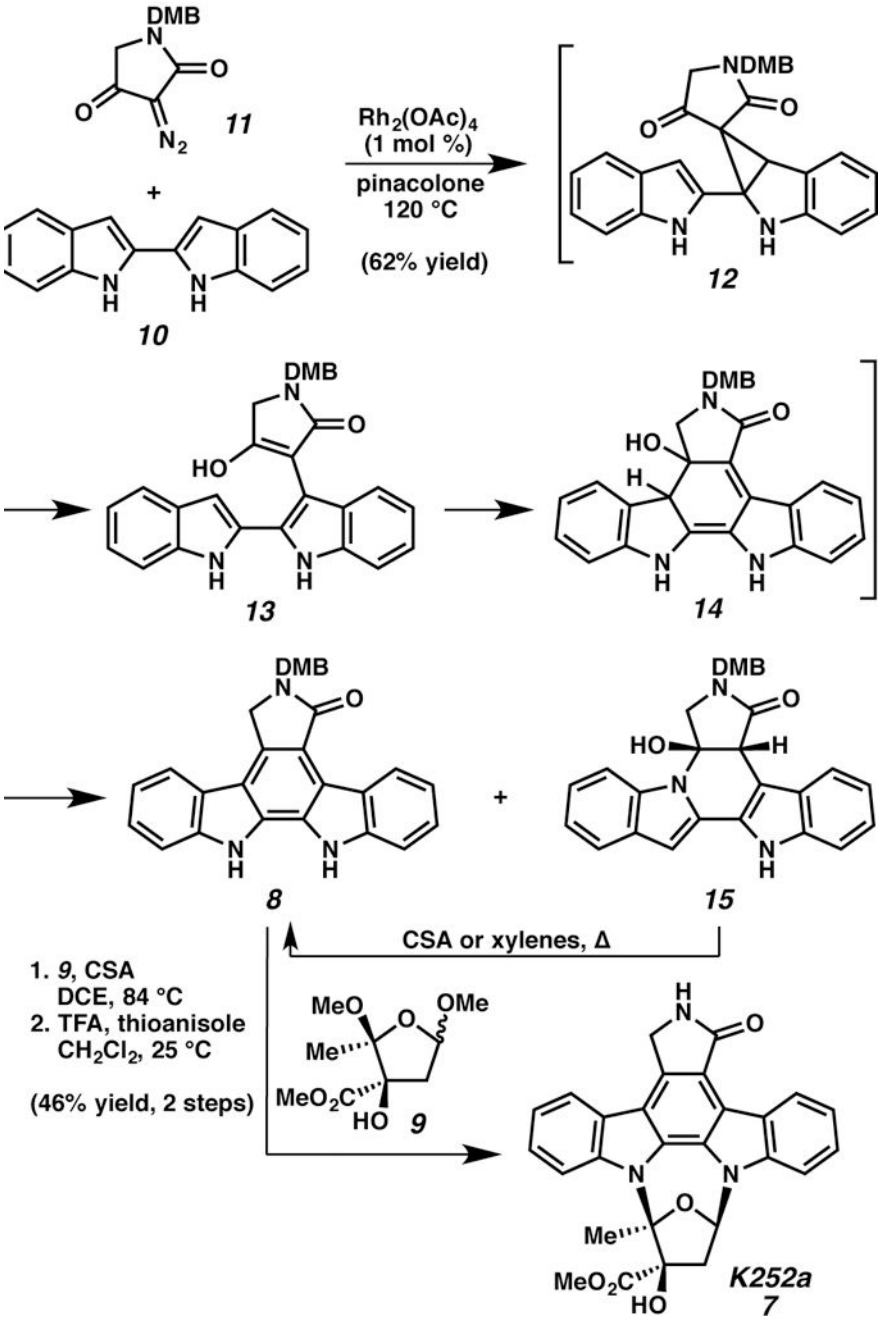


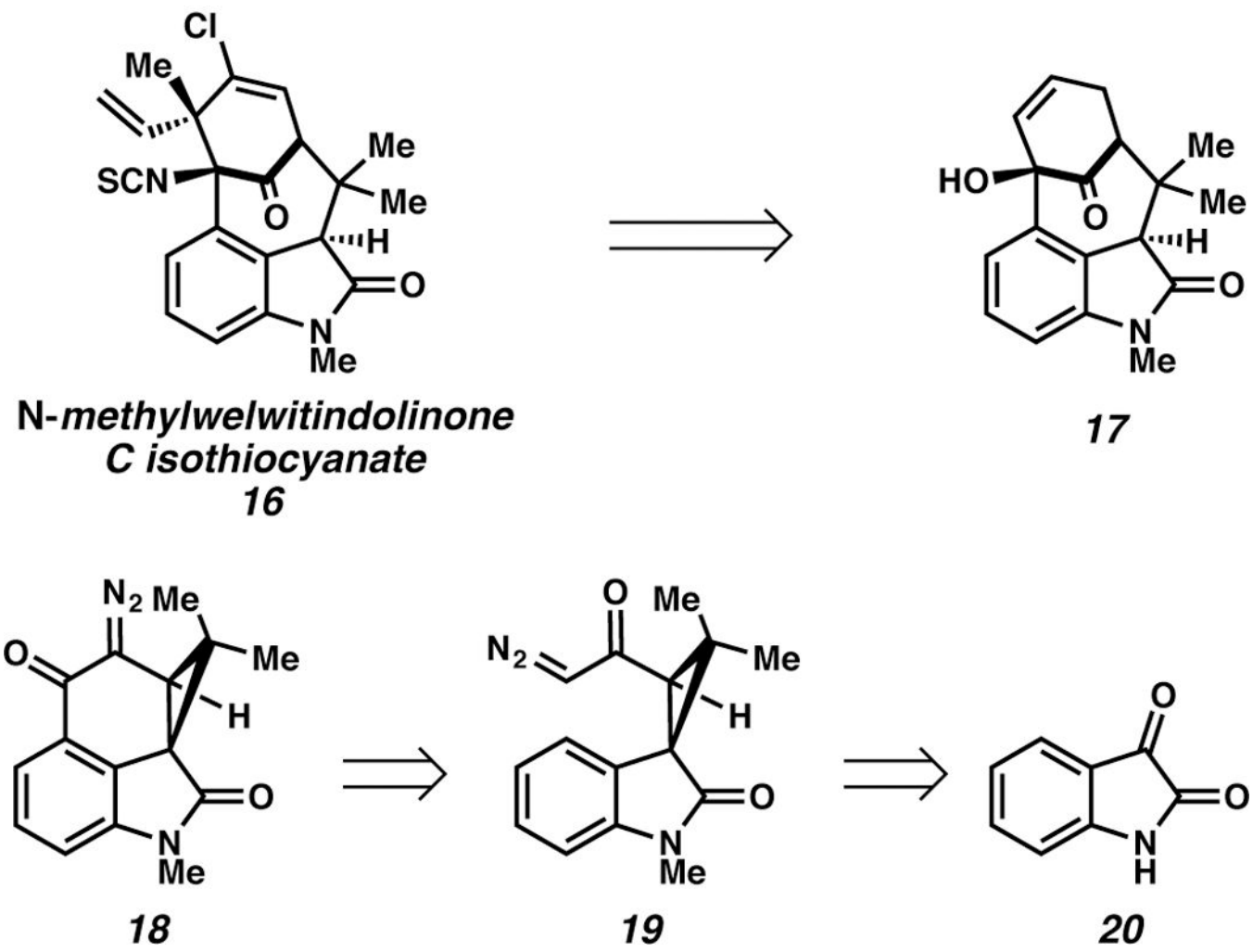
Scheme 1.
Reactivity modes of donor–acceptor cyclopropanes.



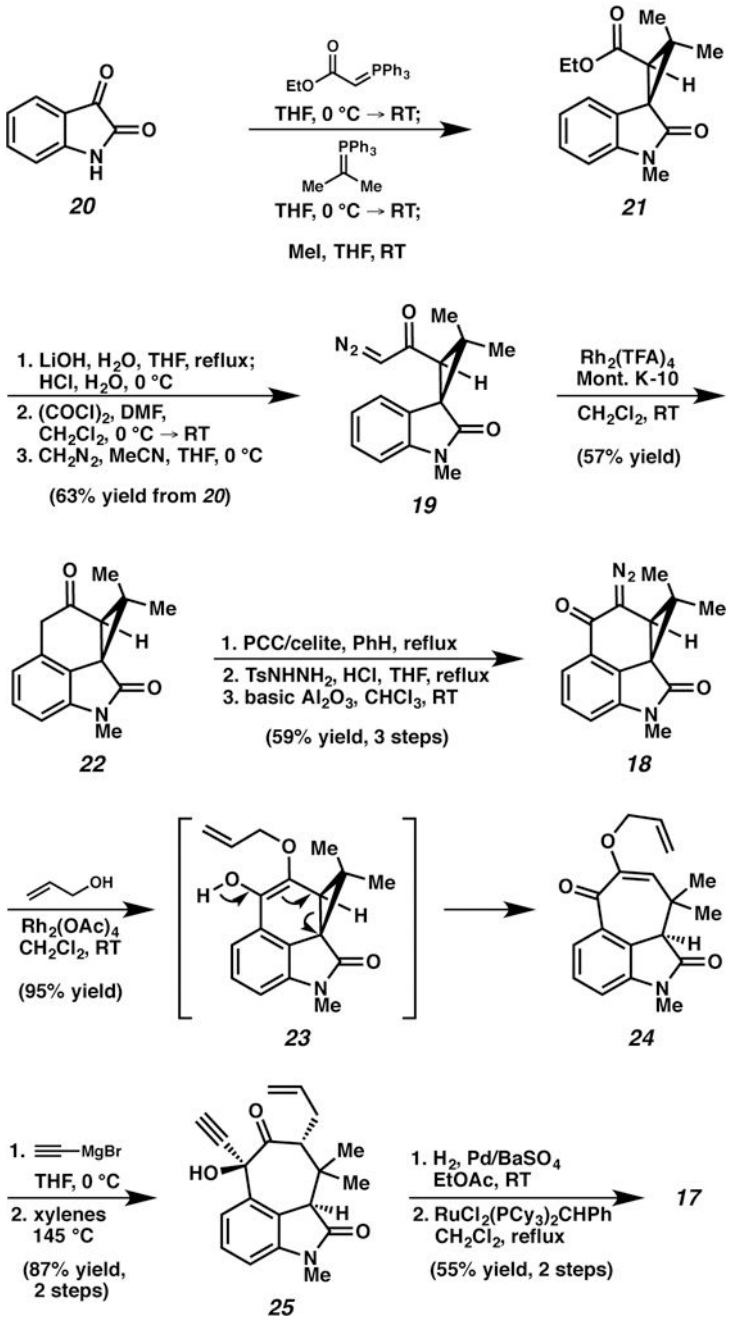
Scheme 2.
Retrosynthetic analysis of K252a.



Scheme 3.
Total synthesis of K252a.

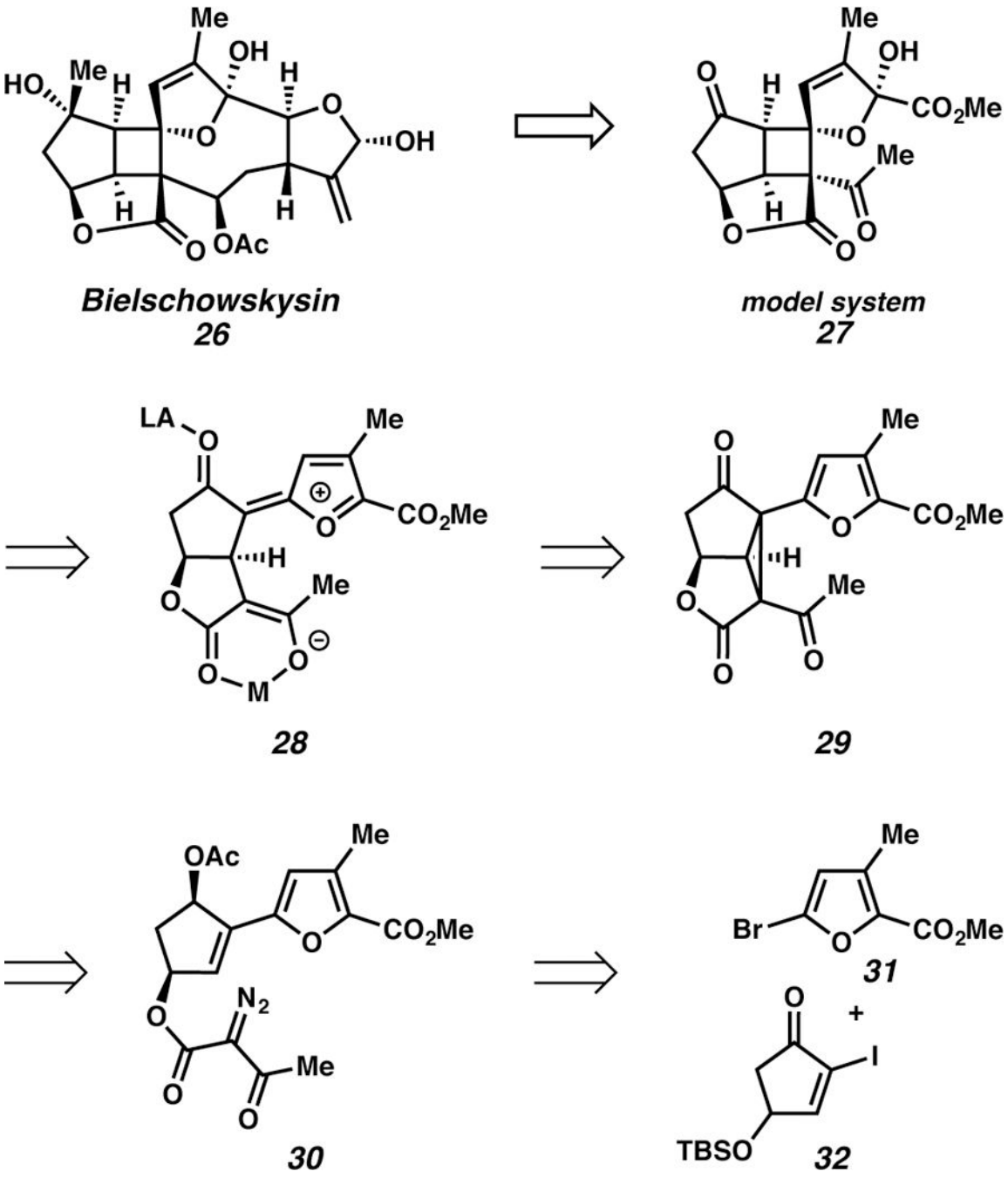


Scheme 4.
Retrosynthetic analysis of *N*-methylwelwitindolinone C isothiocyanate.

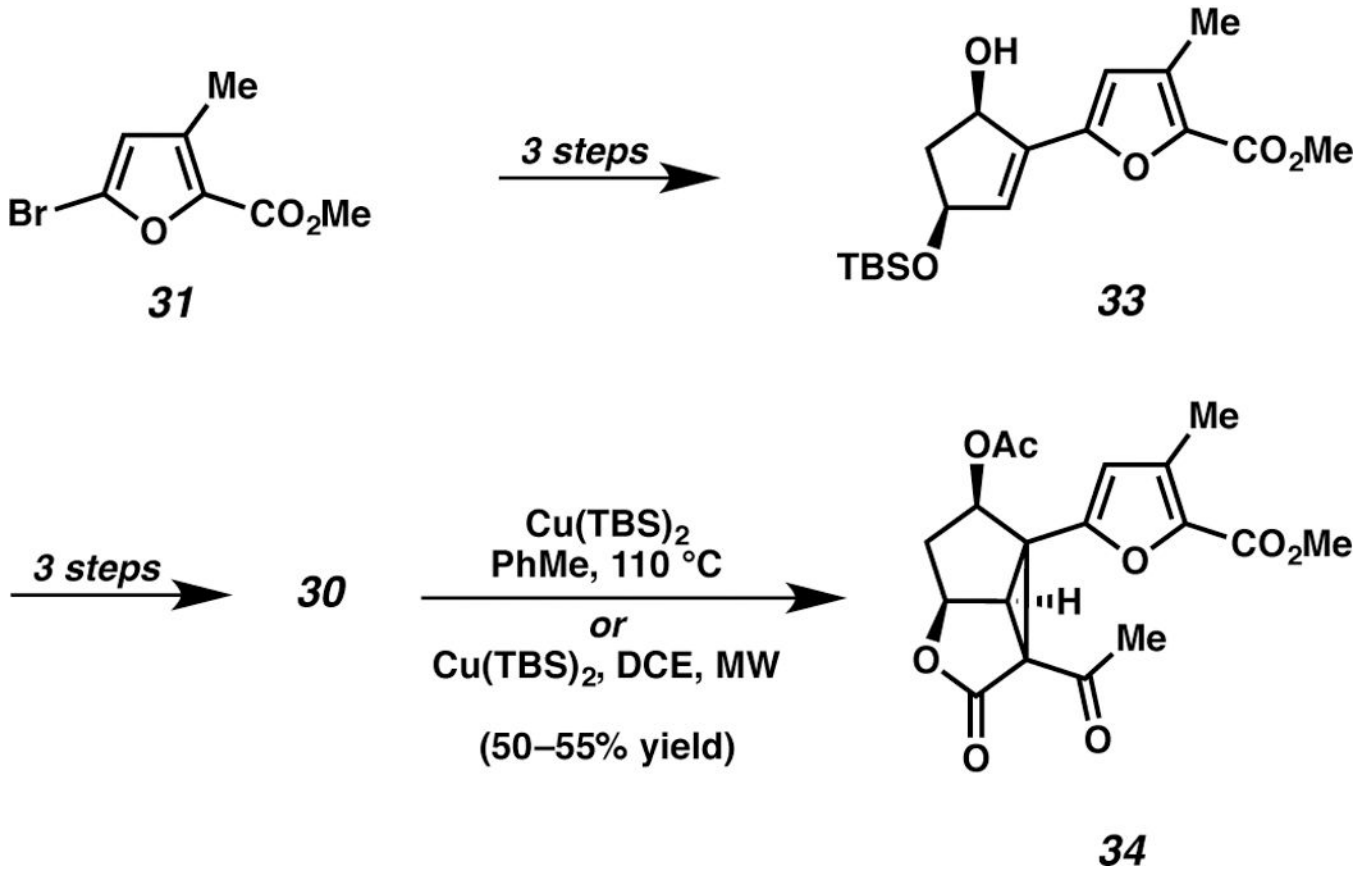


Scheme 5.

Synthesis of the carbon skeleton of Nmethylwelwitindolinone C isothiocyanate

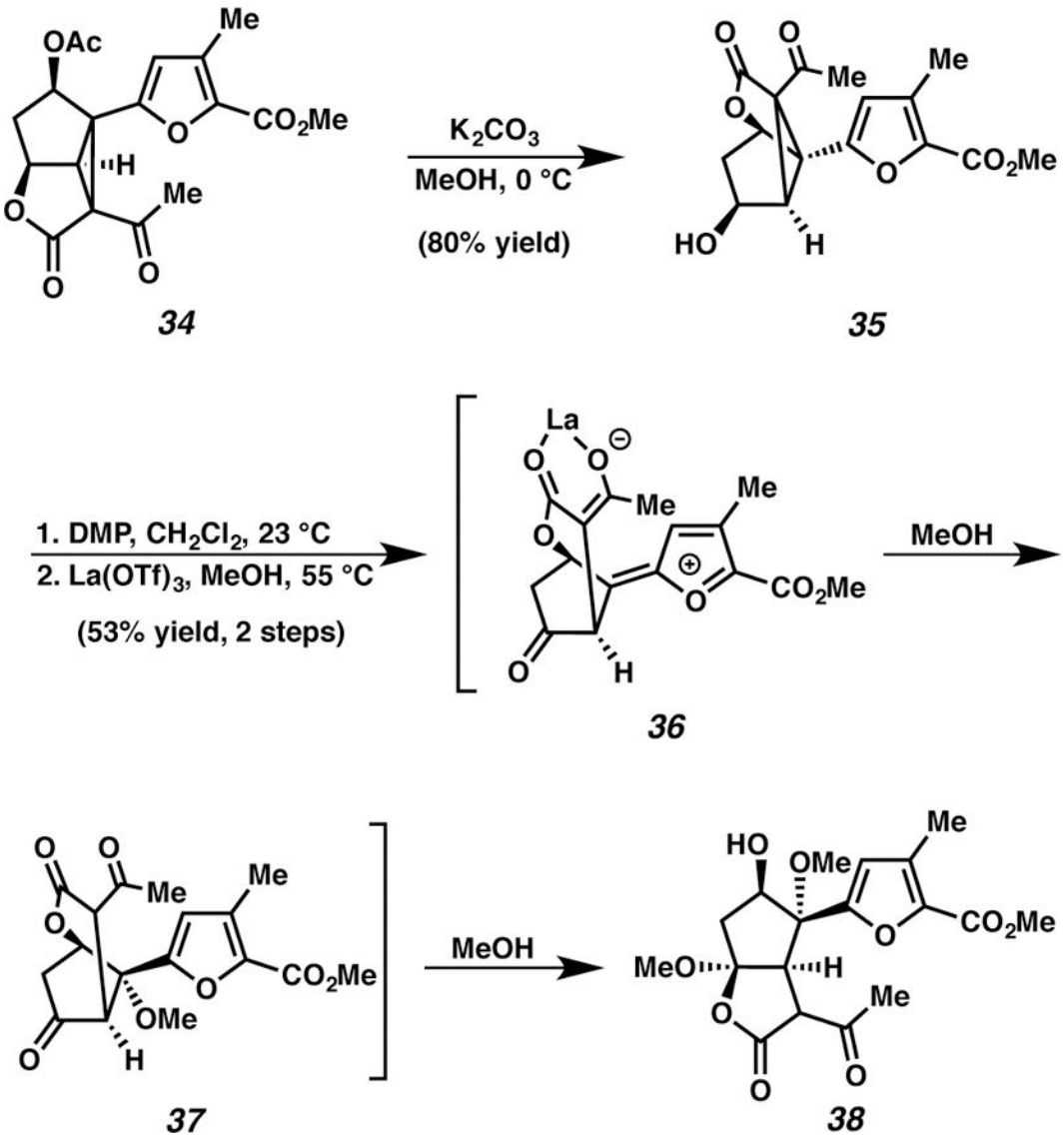


Scheme 6.
Retrosynthetic analysis of bielschowskysin.

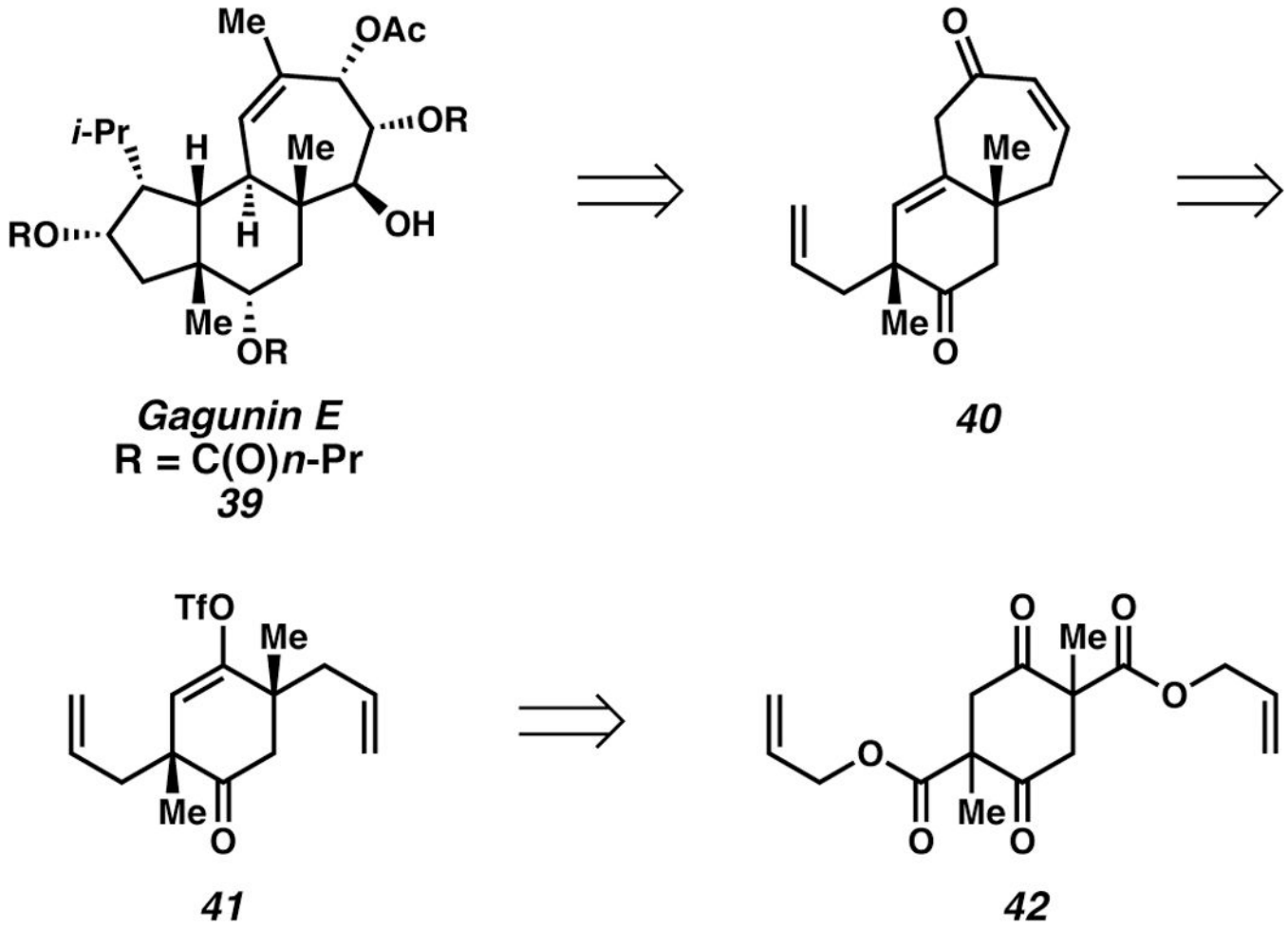


Scheme 7.

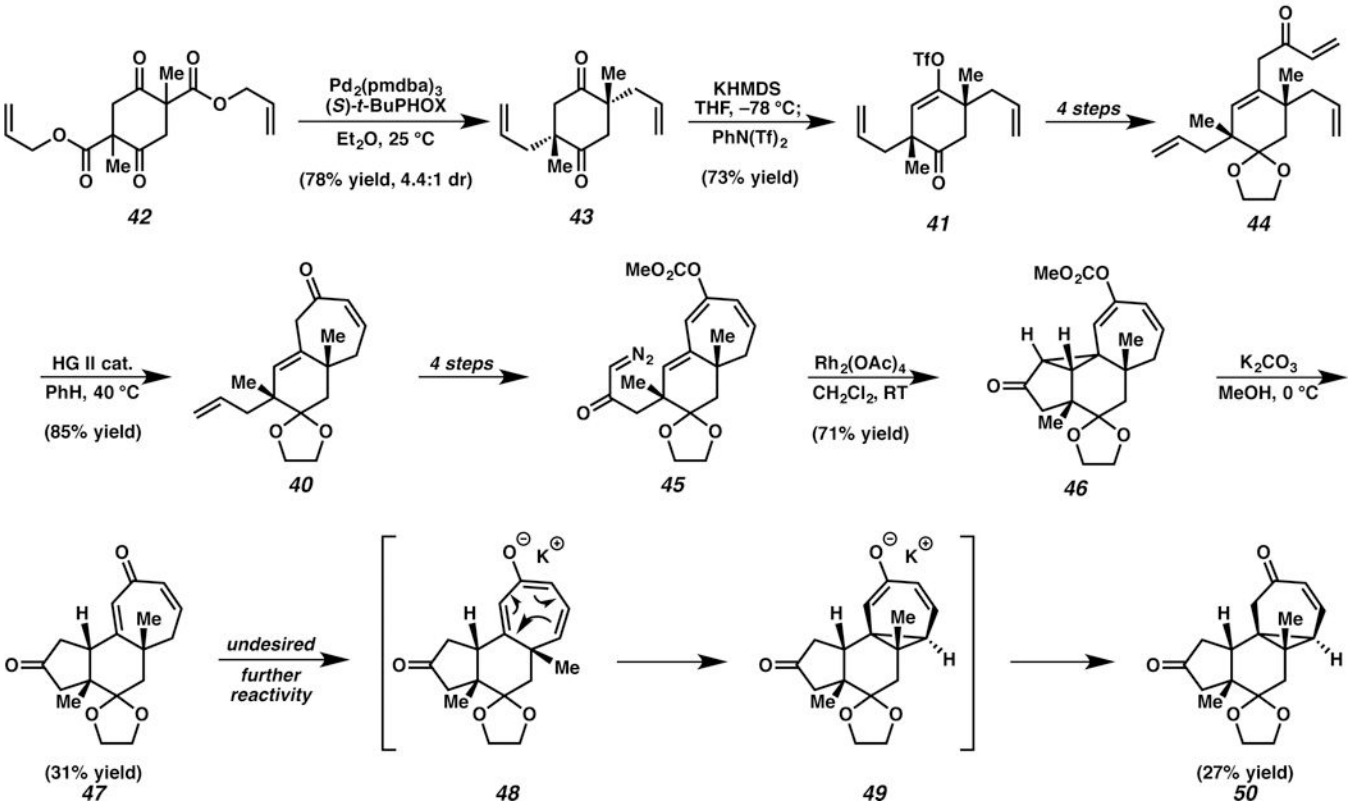
Synthesis of donor–acceptor cyclopropane **34**. Cu(TBS)2 = bis(*N*-*tert*-butylsalicylaldiminato)copper(II).



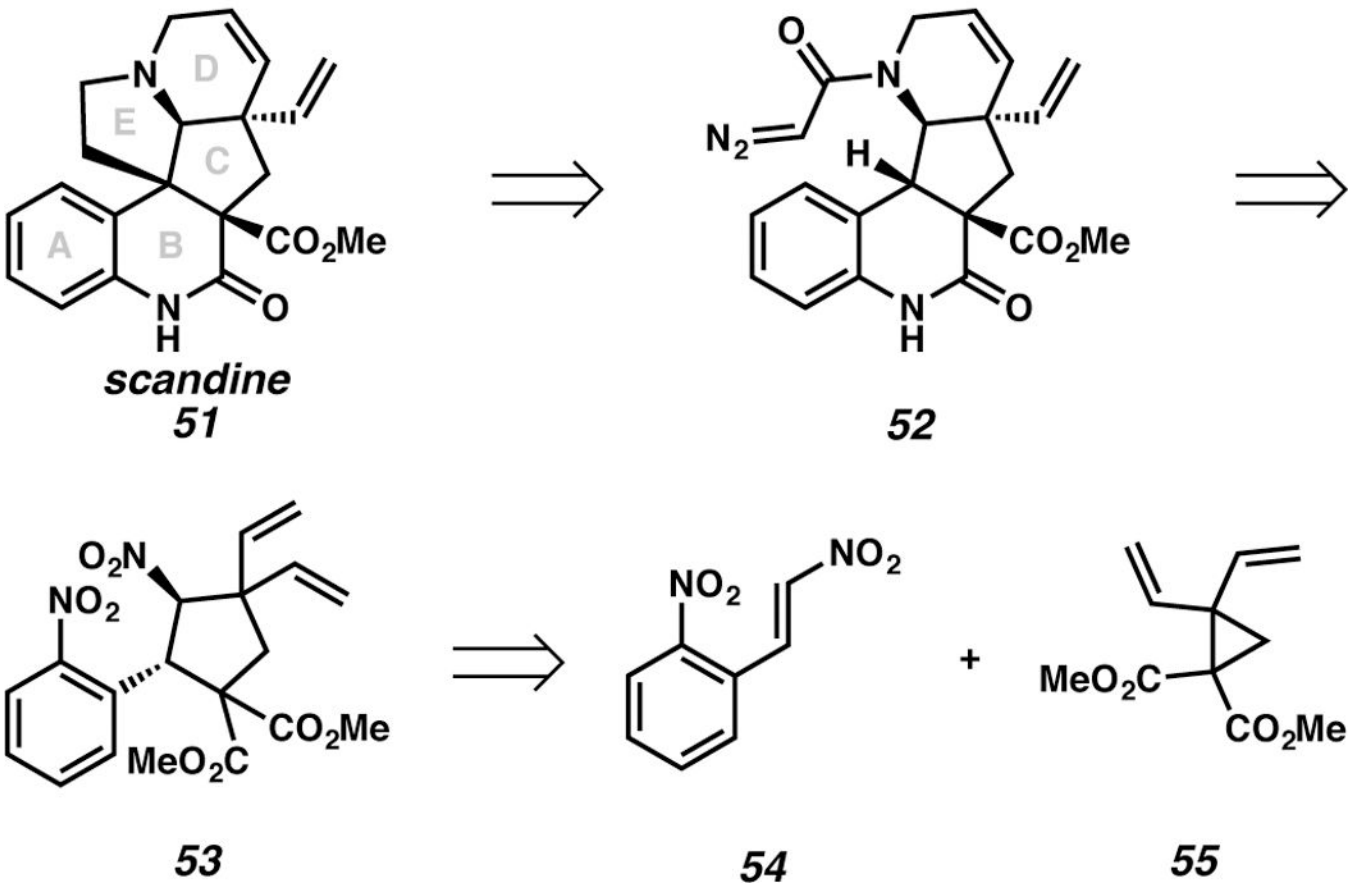
Scheme 8.
Cyclopropane fragmentation.



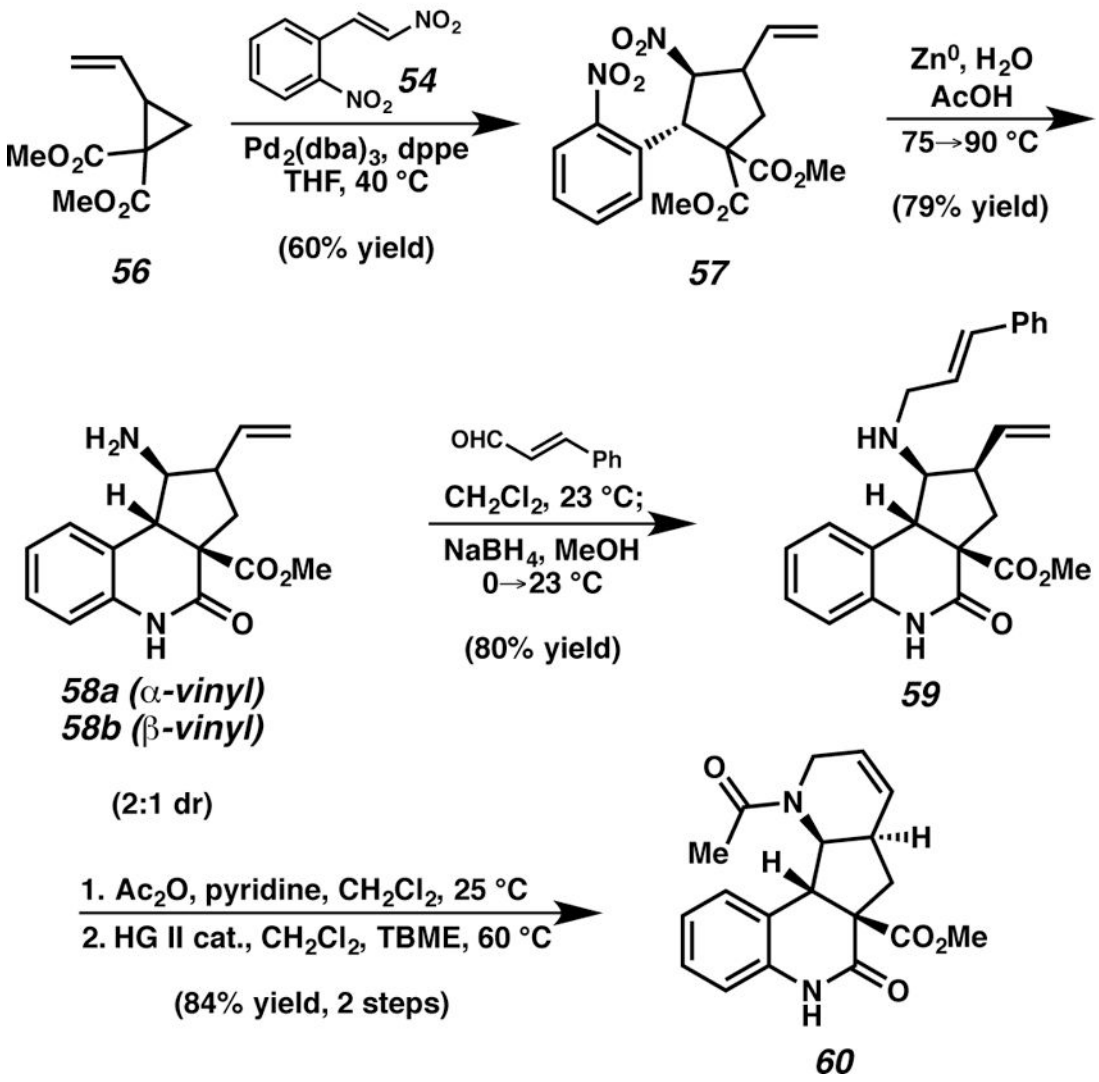
Scheme 9.
Retrosynthetic analysis of gagunin E.



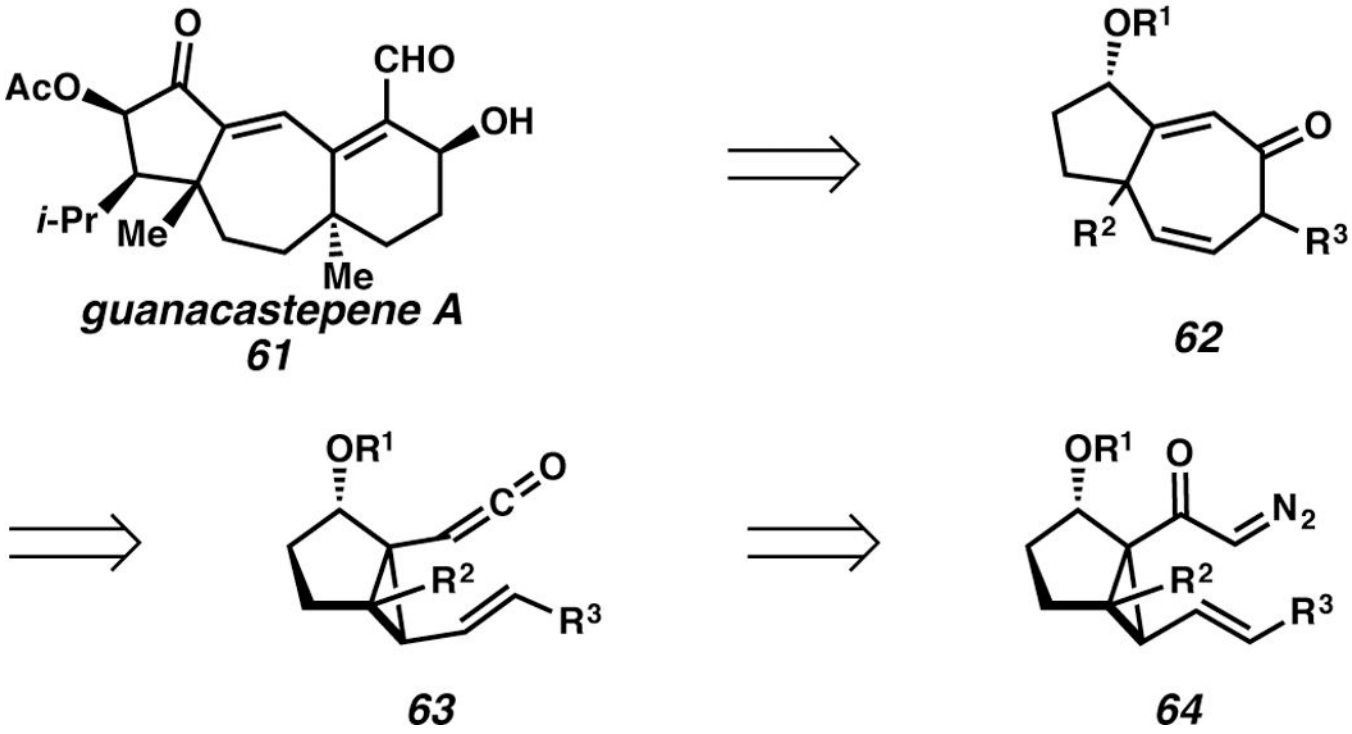
Scheme 10.
Synthesis of the gagunin core.



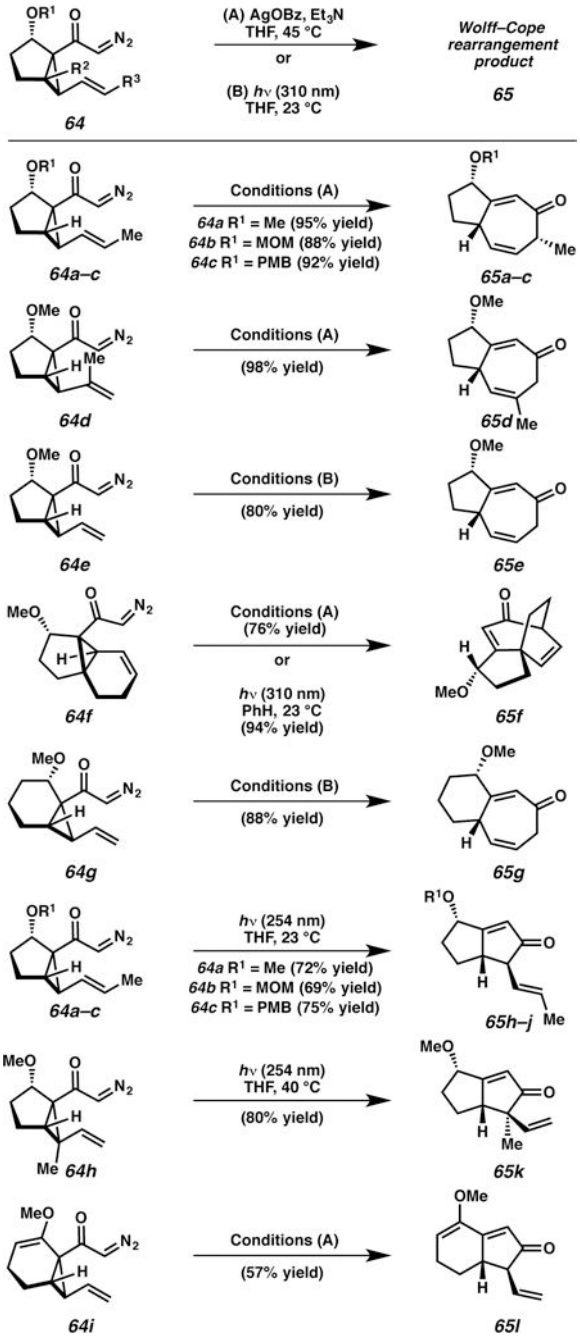
Scheme 11.
Retrosynthetic analysis of scandine.



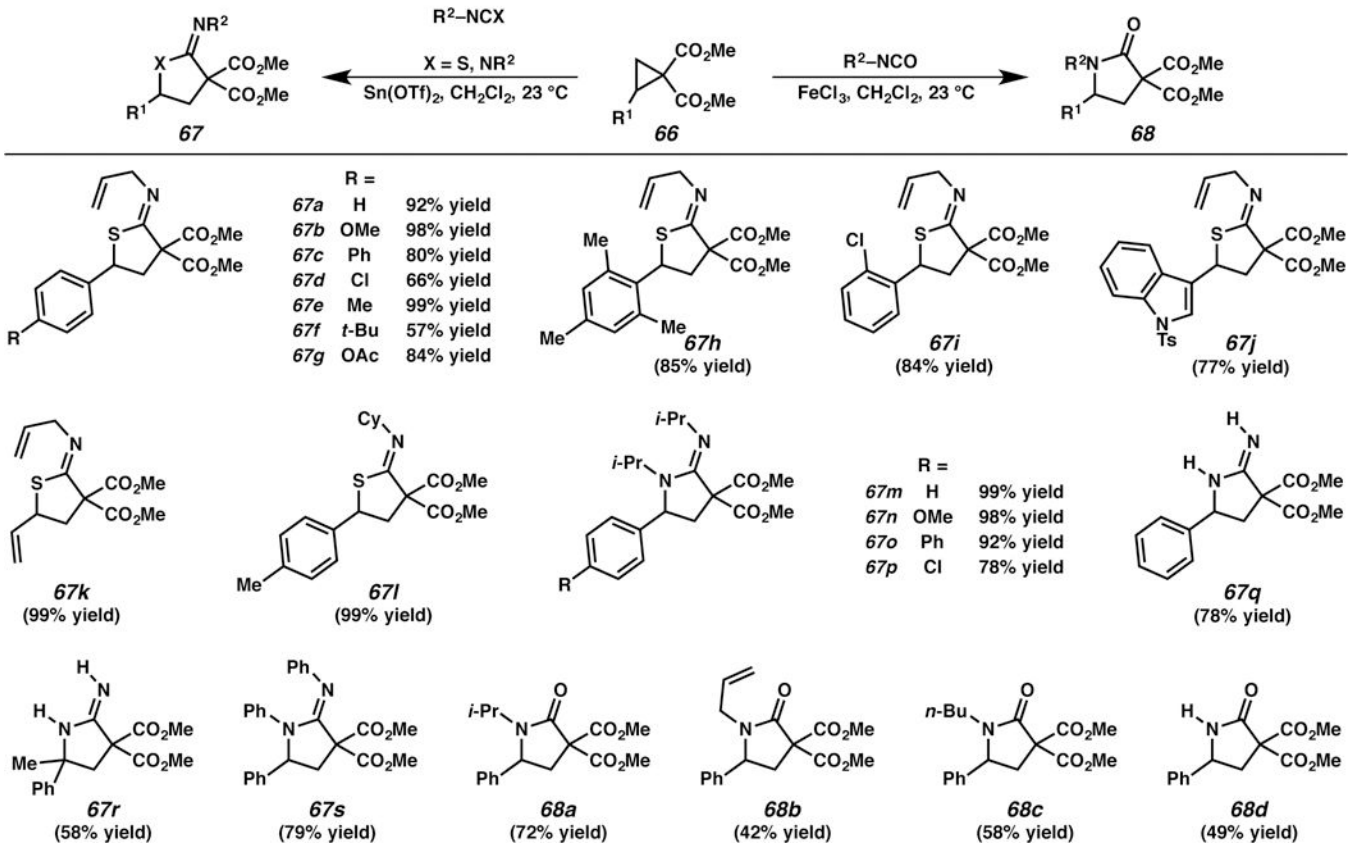
Scheme 12.
Synthesis of the ABCD ring system of scandine.



Scheme 13.
Synthetic inspiration for the tandem Wolff–Cope rearrangement.

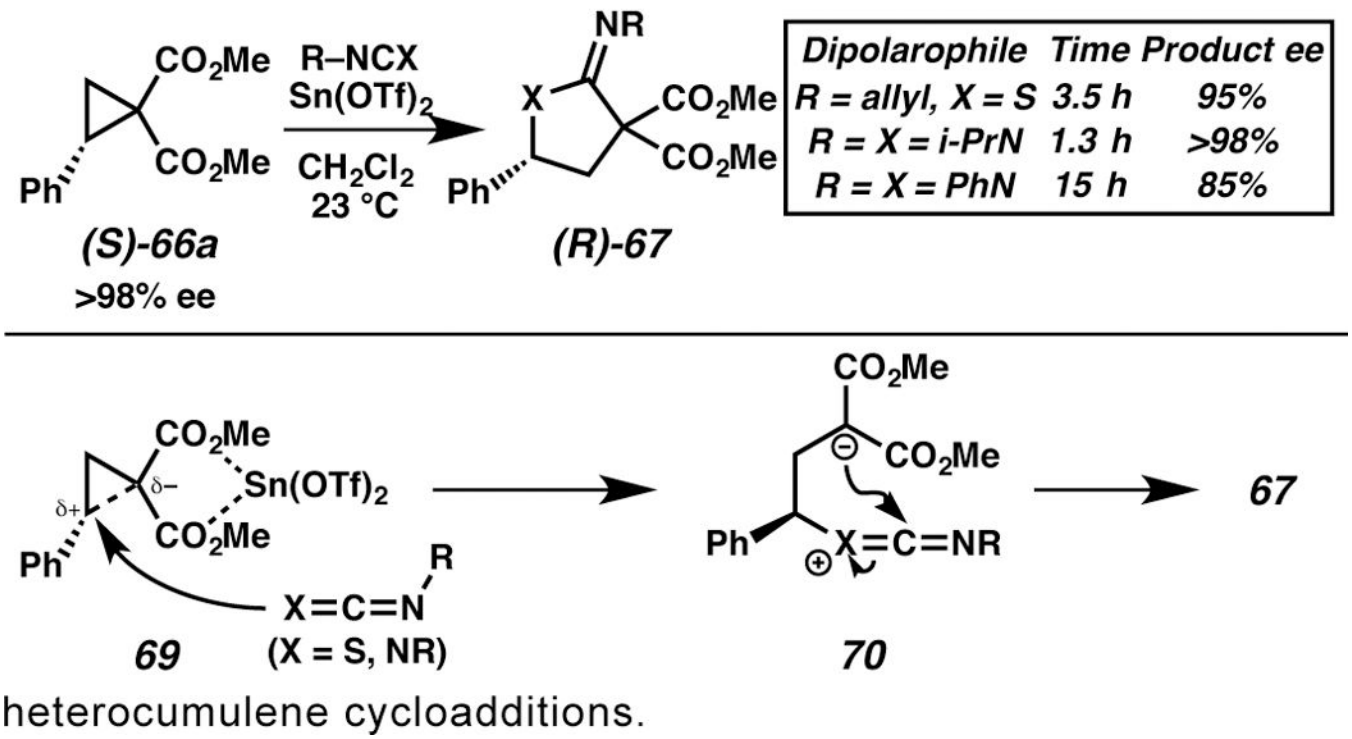


Scheme 14.
Selected scope of the tandem Wolff–Cope rearrangement.

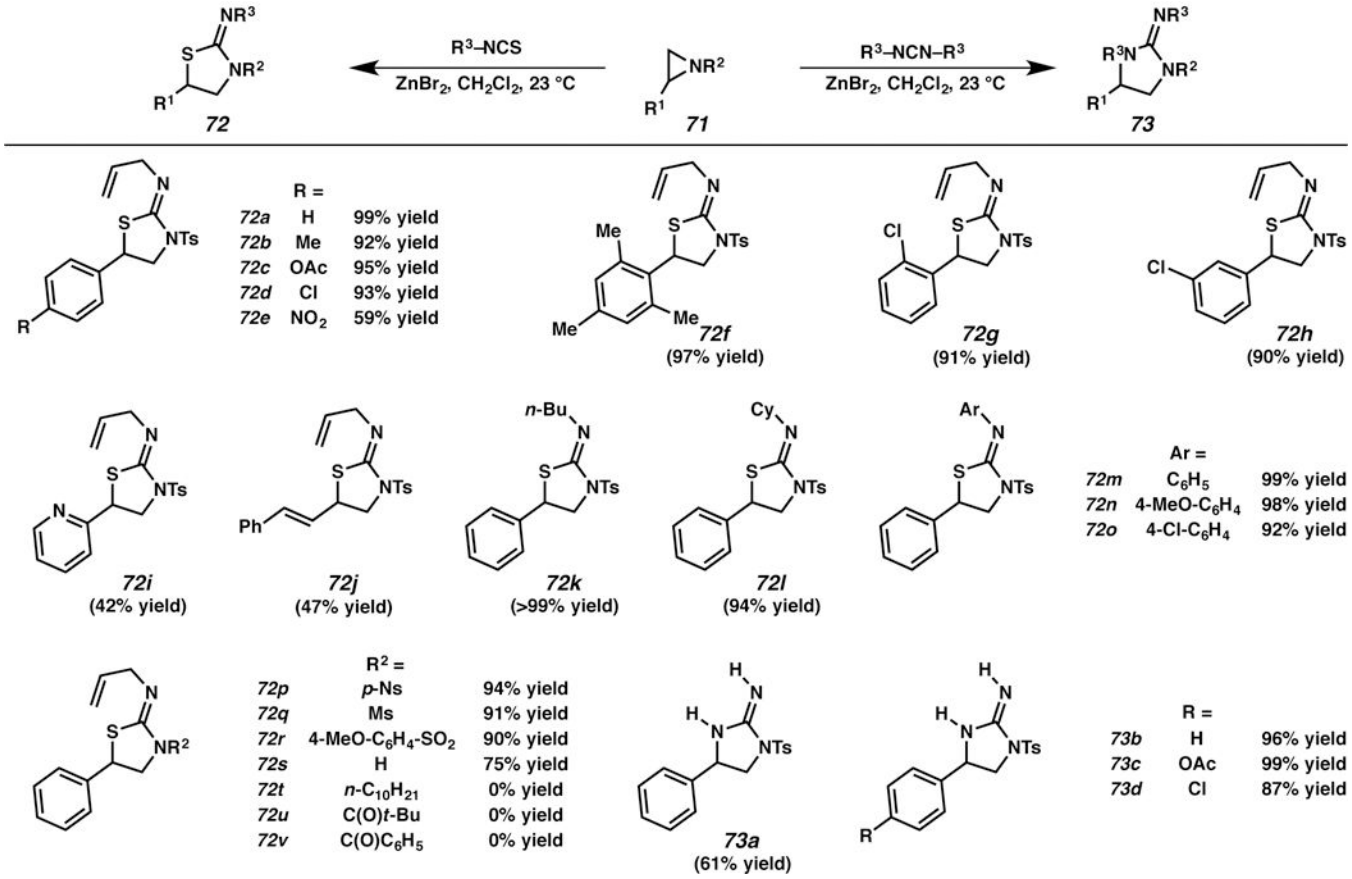


Scheme 15.

Selected scope of cycloadditions of donor–acceptor cyclopropanes with heterocumulenes.

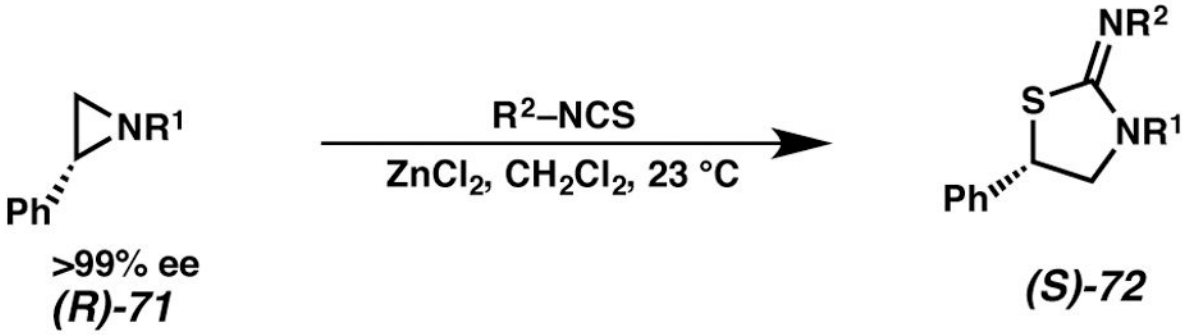


Scheme 16.
Proposed mechanism of cyclopropane-heterocumulene cycloadditions.



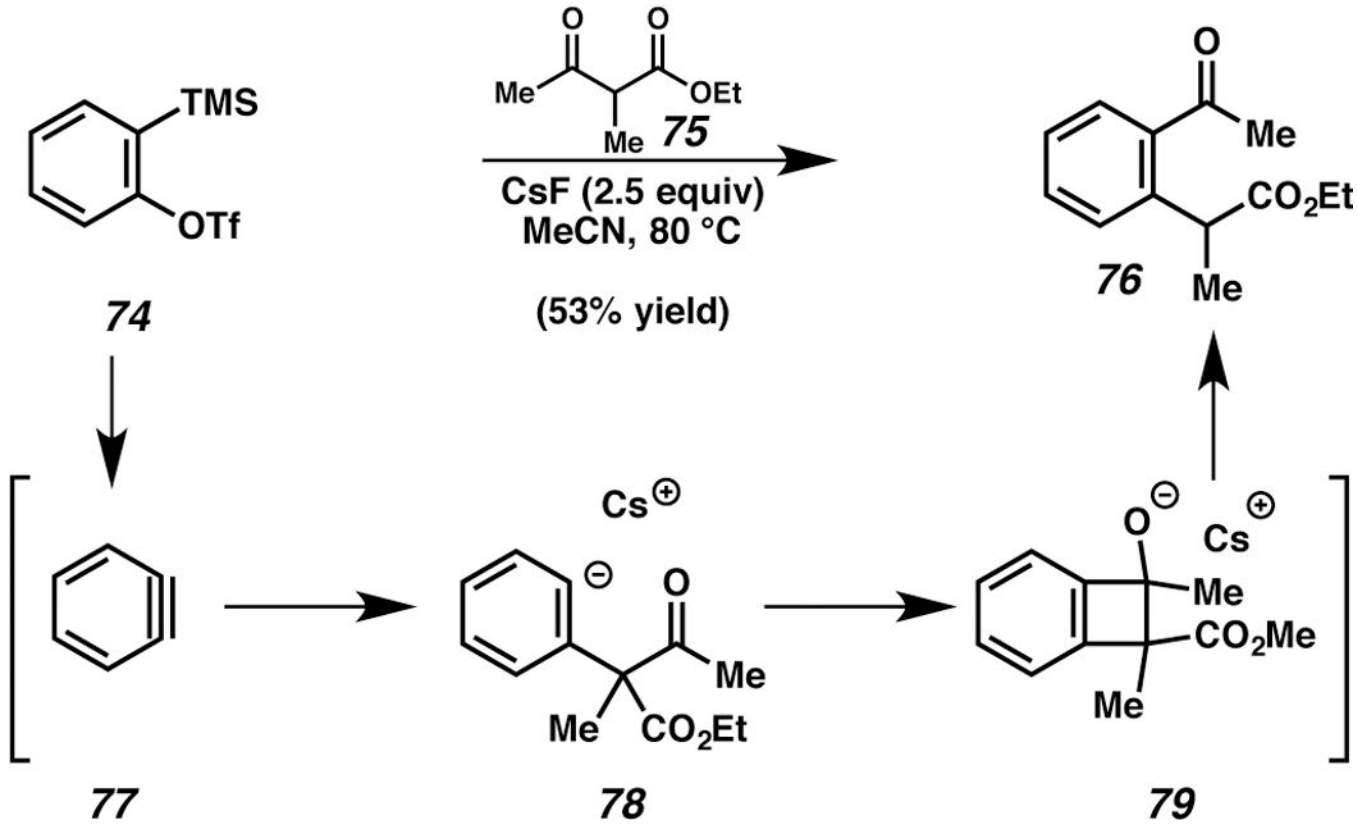
Scheme 17.

Selected scope of cycloadditions of activated aziridines with heterocumulenes.

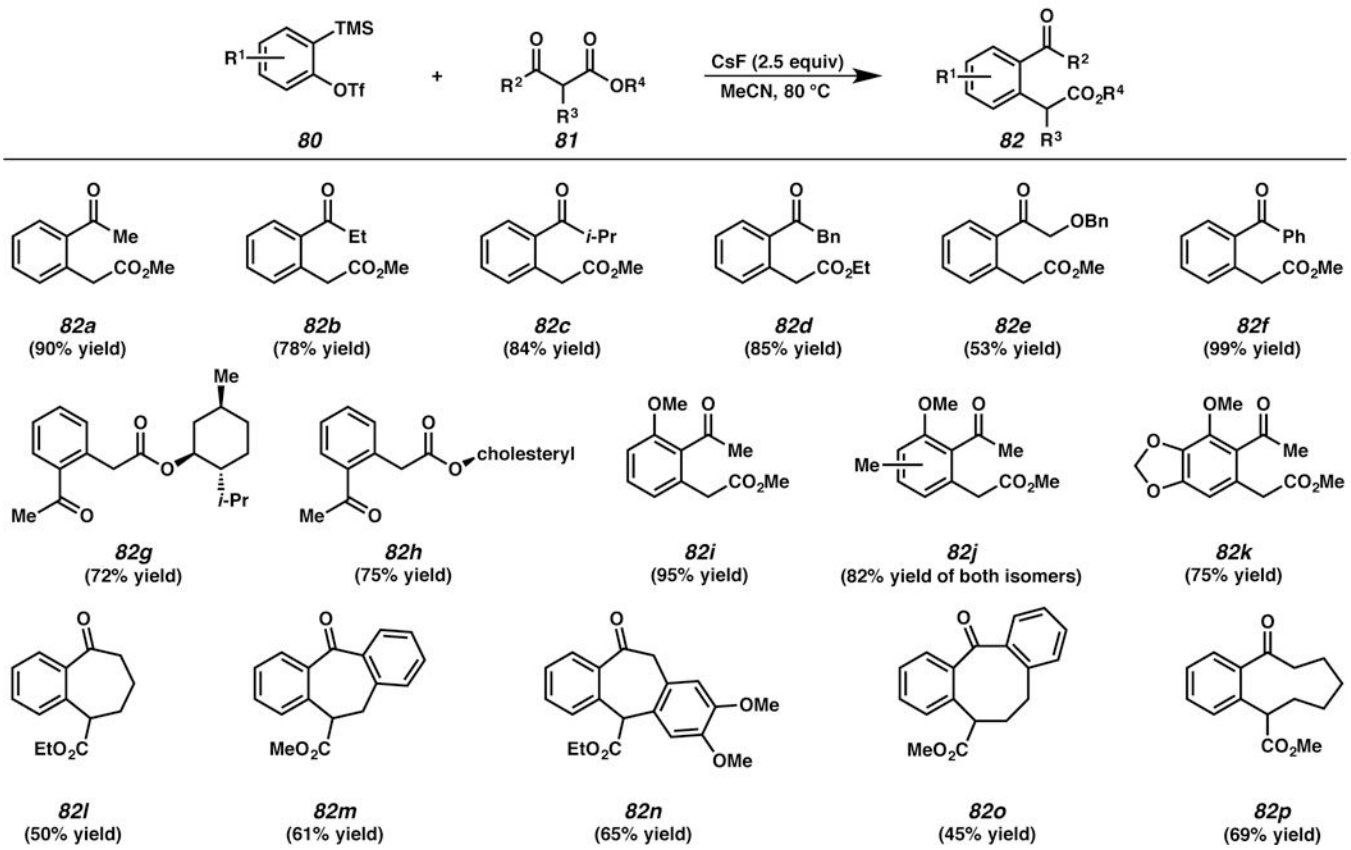


Entry	R^1	R^2	Yield (%)	ee (%)
1	Ts	allyl	99	94
2	Ts	*n*-Bu	94	95
3	Ts	Cy	98	92
4	Ts	*t*-Bu	39	75
5	Ts	Ph	>99	77
6	Ts	4-MeO-C_6H_4	97	90
7	Ts	4-Cl-C_6H_4	99	60
8	*p*-Ns	allyl	>99	95
9	Ms	allyl	95	90
10	4-MeO-C_6H_4-SO_2	allyl	94	91
11	H	allyl	31	34

Scheme 18.
Scope of the stereoselective cycloaddition of activated aziridines with heterocumulenes.



Scheme 19.
Unexpected aryne C–C insertion and mechanistic proposal.



Scheme 20.

Scope of the acyl-alkylation of arynes.